

TOPIC HIGHLIGHT

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Esophageal capsule endoscopy

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Abstract

Capsule endoscopy is now considered as the first imaging tool for small bowel examination. Recently, new capsule endoscopy applications have been developed, such as esophageal capsule endoscopy and colon capsule endoscopy. Esophageal capsule endoscopy in patients with suspected esophageal disorders is feasible and safe, and could be also an alternative procedure in those patients refusing upper endoscopy. Although large-scale studies are needed to confirm its utility in GERD and cirrhotic patients, current results are encouraging and open a new era in esophageal examination.

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INTRODUCTION

Since its introduction by Iddan *et al*^[1], capsule endoscopy

(CE) has acquired a well-established role in the investigation of suspected small bowel (SB) diseases. In fact, over 500 000 CE-procedures have been performed worldwide. Demands for CE are hoped to increase because of its proven superiority to conventional techniques for small bowel examination^[2-11] and emerging indications, such as esophageal capsule endoscopy (ECE) and colon capsule endoscopy. Currently, upper endoscopy (EGD) is considered by most authors as the best method to explore the esophagus. However, because of the discomfort of intubation, conscious sedation is usually required resulting in increased costs, risks and patients acceptability^[12-14]. In fact, because of these concerns, some patients are reluctant to undergo EGD even when it is indicated. So, it seems that there is a need for an alternative, simple and less invasive diagnostic tool for the evaluation of patients with known or suspected esophageal disorders. The esophageal capsule (PillCam™ ESO), which was approved by the FDA in November 2004, allows direct visualization of the esophagus without the need of sedation. Advantages include also its invasiveness and painless nature, the ability to pursue normal daily activities after the procedure and patients acceptability. Clinical data on its use and current indications, although quite limited, have opened a promising era for esophageal endoscopic examination.

PILLCAM™ ESO

The PillCam™ ESO (Given Imaging Ltd. Yoqneam, Israel) is an ingestible and disposable capsule measuring 11 mm × 26 mm (similar to PillCam™ SB) that acquires video images from both ends at a combined rate of 14 frames per second (7 from each side of the capsule) during its natural passage through the esophagus (Figure 1). The battery expires in 20-30 min approximately, resulting in more than 15 000 images captured per procedure, which are usually enough to explore the entire esophagus and sometimes, part of the stomach. The images, transmitted via digital radio frequency communication channel to the data recorder unit located outside the body, are captured by an antenna array located on the upper chest and the abdominal wall of the patient. Upon completion of the procedure, the images are transmitted to the Rapid® Workstation for processing and interpretation, which takes only a few minutes. Recently, a new complementary tool has been developed by Given Imaging: the RAPID® Access



Figure 1 PillCam™ ESO.

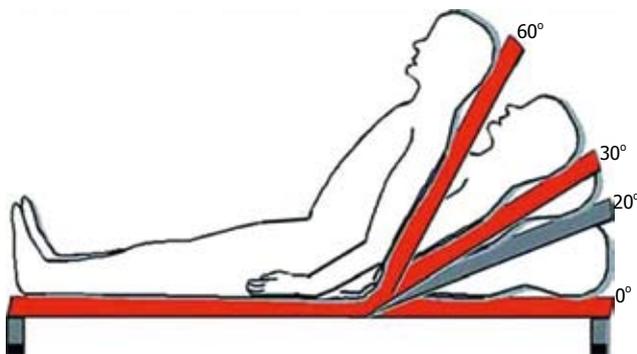


Figure 2 Ingestion protocol.

RT. During the ECE-procedure, the RAPID® Access RT allows real time visualization of capsule images. This is extremely useful in certain circumstances as the physician can intervene to optimize the procedure by changing patient position or administering medications such as laxatives depending on the images obtained in real time.

PROCEDURE

ECE is a quite simplex procedure, which can take only 4-5 min to physicians. This procedure requires implementation of a specific ingestion procedure to assure effective coverage of the esophagus (Figure 2). After a 6 h fast and before capsule ingestion, the patient is asked to drink swiftly a small amount of water (100 mL) in a standing position to clear saliva from the esophagus. Then, the capsule is swallowed in the supine position helped by a small sip of water (10 mL) if required. The patient must remain in this position for 2 min and then must be rose to an inclination of 30 degrees. The patient must remain in this position for 2 min and then the inclination must be increased to 60 degrees. One minute later, the patient is asked to drink a small sip of water (10 mL) and then, allowed to sit upright and to drink again 10 mL of water. In this moment, the patient is allowed to get up and walk in the waiting room for 15-20 min. During procedure in bed, the patient is instructed not to talk. Once the batteries have expired, the procedure is over and downloading



Figure 3 A: PillCam™ ESO image of erosive esophagitis; B: Upper endoscopy image of distal esophagus in the same patient.

process begins (4-5 min). Recently, an article published by Gralnek *et al*^[15] has evaluated a new simplified ingestion procedure (SIP) in healthy volunteers who swallowed the capsule in the right supine position. Although esophageal transit time was shorter in comparison with the original ingestion procedure (mean: 38 s *vs* 225 s, respectively; $P < 0.001$), results showed that the SIP provides significantly improved visualization of the Z-line (visualization of ≥ 2 quadrants of the Z-line in 100% *vs* 75% of the cases; $P = 0.025$). Therefore, the authors recommend testing the proposed SIP in patients undergoing ECE.

ECE IN GERD PATIENTS (TABLE 1, FIGURES 3 AND 4)

Persistent heartburn is one of the most frequent gastrointestinal symptoms in western countries. Symptomatic GERD affects at least 5%-7% of the global population and in western countries, up to 30% of the population is affected by this disorder^[16-18]. Complications of GERD include erosive esophagitis, ulcers, strictures or Barrett's (BE) esophagus. Up to 30% of subjects with GERD are found to have esophagitis while ulcers or strictures occur in 5% of patients^[19]. Barrett's esophagus, which carries a risk of 0.5% per patient-years of esophageal adenocarcinoma, may occur in up to 10% of patients with chronic GERD^[20]. Therefore, international guidelines recommend screening EGD in all GERD patients. However, as demonstrated, its cost and invasiveness limits its utilization in many patients^[21].

Table 1 ECE in GERD patients: results in published studies

Author	Yr	n	Indication	Capsule	Ingestion	S (%)	E (%)	PPV (%)	NPV (%)
Neu ^[22]	2003	8	Esophagitis	SB	Supine	37.5	(-)	(-)	(-)
Ramirez ^[23]	2005	50	BE	String SB	Standing	100	100	100	100
Eliakim ^[24]	2004	17	Esophagitis BE	ESO 4-fps	Supine	100	80	92	100
Eliakim ^[25]	2005	93	Esophagitis	ESO 4-fps	Supine	89	99	97	94
Eliakim ^[25]	2005	13	BE	ESO 4-fps	Supine	97	99	97	99
Koslowsky ^[26]	2006	25	Esophagitis BE	ESO 4-fps	Supine	81	61	74	79
Koslowsky ^[26]	2006	25	Esophagitis BE	ESO 14-fps	Supine	100	74	100	77
Sharma ^[27]	2007	53	BE (suspected-known)	ESO 14-fps	Supine	67-79	87-78	60-94	90-44
Sharma ^[27]	2007	41	Esophagitis	ESO 14-fps	Supine	50	90	56	88
Lin ^[28]	2007	90	BE	ESO 14-fps	Supine	67	84	22	98

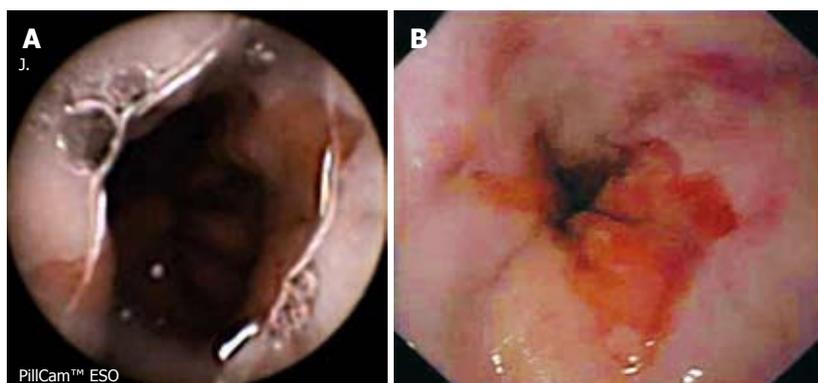


Figure 4 A: PillCam™ ESO image of short segment Barrett's esophagus; B: Subsequent upper endoscopy image which confirms capsule findings.

In 2003, Neu *et al*^[22] published the first article regarding ECE. Using SB capsules (single camera at a frame rate of 2/s), they evaluated the accuracy of capsule endoscopy in 8 patients with known esophagitis. All patients swallowed the capsule in the supine position. The capsule detected only 3 of 8 (37.5%) patients with esophagitis and an adequate visualization of 50% and 100% of the Z-line circumference was achieved in 12.5% and 37.5% of the patients, respectively. They also evaluated the quality of images obtained by the capsule in 58 patients examined for suspected small bowel pathology with poor results (0% of 100% of the Z-line circumference visualization), due to the short esophageal transit time (these patients swallowed the capsule in standing position). They concluded that distal esophageal assessment by SB capsules was not feasible.

Few months later, Ramirez *et al*^[23] used SB capsules attached to strings allowing capsule control up and down the esophagus. Fifty patients with Barrett's esophagus were enrolled in this study. The mean recording time in this study was much longer than in the previous study by Neu *et al* (7.9 min *vs* 3 s). All 50 patients with BE were detected by the capsule. The majority of patients (92%) preferred string-capsule endoscopy to EGD because usually, none or minimal discomfort was associated with capsule ingestion. They concluded that string esophageal capsule endoscopy is feasible, safe and highly acceptable by patients with esophageal disorders.

In 2004, Eliakim *et al*^[24] published a pilot study of ECE using specifically-designed capsules for esophageal examination (double camera at a frame rate of 4 per second). They compared the diagnostic yield of ECE to EGD (used as gold standard) in 17 patients with

suspected esophageal disorders. All patients swallowed the capsule in supine position to avoid rapid esophageal transit of the capsule. All patients with positive findings at EGD (12/17) were detected by the capsule. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 100%, 80%, 92% and 100%, respectively. Of 15 patients asked, 12 (80%) preferred the capsule experience to EGD which was performed under sedation with Midazolam 2.5-5 mg. They concluded that ECE with the new device proposed is an accurate, convenient, safe and well-tolerated method for patients with esophageal disorders. These results were encouraging but the small sample size of this pilot study was an obstacle to elaborate solid conclusions. Then, largescale studies seemed to be necessary.

A similar study conducted at 7 sites in 2005^[25] evaluated the new developed PillCam™ ESO (double camera at a frame rate of 4 per second) compared to EGD in 106 patients (93 with GERD and 13 with BE). All patients swallowed the capsule in the supine position. Sensitivity, specificity, PPV and NPV for esophagitis were 89%, 99%, 97% and 94%, respectively, and 97%, 99%, 97% and 99%, respectively, for BE. ECE was preferred over EGD by all patients. These results were consistent with those obtained by Eliakim *et al*^[24] in 2004. They concluded that ECE was a convenient and sensitive method for visualization of esophageal mucosal pathology and may provide an effective method to evaluate patients for esophageal disease.

However, some experiences have shown that the speed of the capsule in the proximal esophagus can reach up to 20 cm per second. It means that using the

Table 2 ECE in portal hypertension: Results in published studies

Author	Yr	n	Indication	Capsule	Ingestion	S	E	PPV	NPV
Ramirez ^[40]	2005	30	Varices	String SB	Standing	96%	100%	100%	83.3%
Eisen ^[41]	2006	32	Varices	ESO 14-fps	Supine	100%	89%	(-)	(-)
Eisen ^[41]	2006	32	PHG	ESO 14-fps	Supine	100%	77%	(-)	(-)
Lapalus ^[42]	2006	21	Varices	ESO 14-fps	Supine	81.2%	100%	100%	57%

4-frame per second capsule, only one image could be taken per 10 cm length in some instances. Koslowsky *et al*^[26] speculated in 2006 that the diagnostic yield of the ECE might be improved by using a 14-frame per second capsule. Fifty patients (42 suffering from GERD symptoms and 8 with confirmed BE) were included in this study and all of them swallowed the capsule in the supine position: 25 underwent ECE with the 4-frame per second capsule and 25 underwent ECE with the 14-frame per second capsule. Using EGD as gold standard, the 4-frame per second capsule sensitivity, specificity, PPV and NPV were 81%, 61%, 74% and 79%, respectively, and the 14-frame per second capsule sensitivity, specificity, PPV and NPV were 100% ($P < 0.02$), 74%, 100% and 77%, respectively. The upper esophageal sphincter and the entire esophagus were assessed by the 4-fps capsule in 25% and 12% of the cases, respectively, and in 81% ($P < 0.01$) and 76% ($P < 0.01$) of the cases by the 14-fps capsule, respectively. They concluded that ECE using the 14-fps capsule has a greater sensitivity and allows better visualization of the entire esophagus than the 4-fps capsule.

Recently, two prospective, blinded and well-designed studies have compared the diagnostic accuracy of ECE using the 14-fps capsule *vs* EGD in both GERD and BE. Sharma *et al*^[27] included 100 patients with GERD and BE. Ninety-four of these patients swallowed the capsule in the supine position. Results reported showed a higher diagnostic accuracy for BE than for erosive esophagitis. The sensitivity, specificity, PPV and NPV for BE in GERD patients were 67%, 87%, 60% and 90%, respectively, and for known Barrett's esophagus in patients undergoing surveillance were 79%, 78%, 94% and 44%, respectively. The diagnostic accuracy of ECE for long Barrett's segment esophagus (LSBE) was greater than for short Barrett's segments esophagus (SSBE). For erosive esophagitis, the sensitivity was 50%, the specificity 90%, the PPV 56% and the NPV 88%. These results were quite different than those obtained in previous studies. These differences might be attributed in part, to the diagnostic skills of examiners and to the ingestion protocol in the supine position. Anyway, the authors require for the future an improvement in technology and learning curve assessments. The other study, published at the same time by Lin *et al*^[28], included 96 patients with chronic gastroesophageal reflux and BE undergoing surveillance. Again, the selected ingestion protocol was in the supine position. ECE sensitivity, specificity, PPV and NPV for BE were 67%, 84%, 22% and 98%, respectively. There were no differences between SSDE and LSBE detection. These results were

similar to the study by Sharma *et al*^[27] but again, quite different to those showed in previous studies with the 4-fps capsule. The authors attributed these differences to the patient adjudication process in previous studies (unblinded investigators). They conclude that ECE is not, at present, suitable as a primary screening tool for BE but may be used in patients unwilling to undergo EGD. Precisely, one study by Sanchez-Yague *et al*^[29] published in 2006, reviewed 30 cases of ECE in patients refusing conventional endoscopy. They demonstrated that ECE is an adequate alternative diagnostic method for the study of patients with suspected esophageal diseases.

ECE IN PATIENTS WITH PORTAL HYPERTENSION (TABLE 2, FIGURES 5 AND 6)

The presence of esophageal varices is one of the most common complications of portal hypertension in cirrhotic patients. Although they are present in about 50% of the patients when cirrhosis is diagnosed, most of these patients develop varices during their lifetime^[30,31]. Severe upper gastrointestinal bleeding as a complication of portal hypertension occurs in about 30%-40% of cirrhotic patients and in most cases because of the presence of esophageal varices^[32,33]. Despite recent improvements in the diagnosis and treatment of esophagogastric variceal haemorrhage, the mortality rate of first variceal haemorrhage remains high (20%-35%)^[33-36]. The risk of bleeding is related to the hepatic venous pressure, the Child- Pugh class and the endoscopic appearance of the varices^[37]. Therefore, one of the challenges is to identify those cirrhotic patients who have esophageal varices and are also at risk of bleeding. Recently, the Baveno III Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened by means of upper endoscopy for esophageal varices when liver cirrhosis is diagnosed, at 2-3 years intervals in compensated patients without varices and at 1-2 years intervals in compensated patients with previous small varices^[38]. However, sedation during EGD in cirrhotic patients carries increased risks of cardiopulmonary complications because they are more susceptible to oversedation than those with normal liver function^[12,39].

At the moment, three published studies have evaluated the role of ECE in portal hypertension. The first study was published in 2005 by Ramirez *et al*^[40] who used the string-capsule endoscopy to evaluate portal

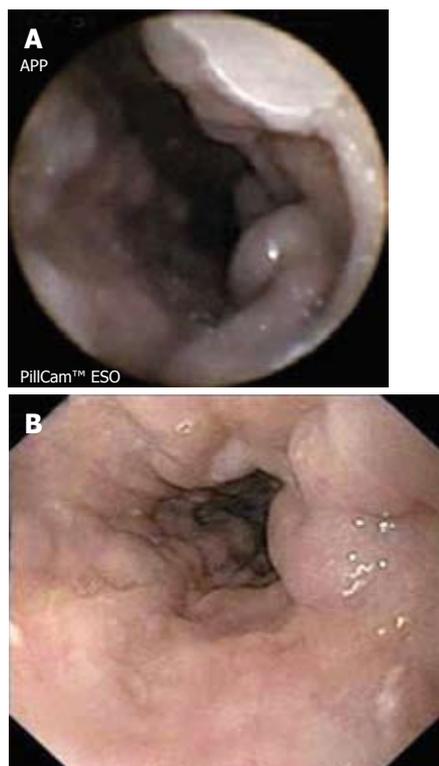


Figure 5 A: PillCam ESO™ image showing esophageal varices; B: Upper endoscopy image of distal esophagus in the same patient.

hypertension in 30 cirrhotic patients. They reported an overall accuracy of 96.7% for varices (sensitivity of 96%, specificity of 100%, PPV of 100% and NPV of 83.3%, respectively) and all patients preferred string-capsule endoscopy to EGD.

On the other hand, two comparative studies have been recently published. Both of them used the new 14-fps capsule, which were swallowed in the supine position, and compared ECE *vs* EGD for portal hypertension in cirrhotic patients. Eisen *et al*^[41] included 32 cirrhotic patients who were undergoing EGD for varices screening or surveillance. They reported a sensitivity of 100%, specificity of 89%, positive likelihood ratio of 9.1 and negative likelihood ratio of 0.0 for esophageal varices detection in comparison with EGD. There was complete agreement in the grading of varices in 65% of the cases and in 95% of the cases within one grade. They also evaluated the accuracy of the capsule to detect portal hypertension gastropathy (PHG). Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for PHG were 100%, 77%, 4.3 and 0.0, respectively. This pilot study led to a multicenter study with more than 300 patients included which is now finished but not yet published. The other comparative study by Lapalus *et al*^[42], simultaneously published, included 21 cirrhotic patients who were undergoing unsedated EGD for varices screening. Results showed that ECE accurately assessed the presence of esophageal varices in 85% of the cases and correctly indicated a need for primary prophylaxis in 100% of the cases. All patients preferred ECE to unsedated EGD which was performed with a small-diameter upper gastrointestinal endoscope.

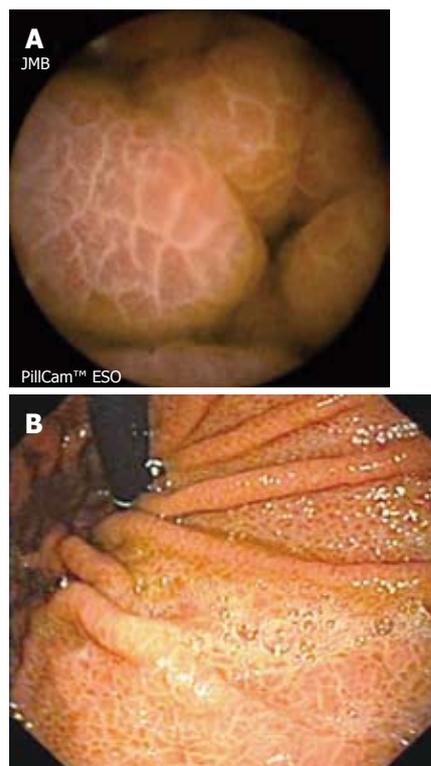


Figure 6 A: PillCam ESO™ image of the gastric wall showing portal hypertension gastropathy; B: Subsequent upper endoscopy image which confirms capsule findings.

CONCLUSION

Capsule endoscopy has opened a new era in small bowel examination. Its indications are now well-defined and currently, wireless capsule endoscopy is considered as the first-line imaging tool for the diagnosis of small bowel diseases. ECE has been shown to be feasible, safe (no ECE-related complications have been reported with the PillCam™ ESO) and a good alternative technique in patients refusing conventional endoscopy. Although results reported in both GERD and cirrhotic patients are encouraging, great differences in terms of accuracy (particularly in GERD patients) have been found in published studies. These differences have been attributed to study designs, the lack of adequate experience and inconvenience of ingestion protocols. In summary, more large-scale studies evaluating the new 14-fps capsule, adequate ECE-experience and new modified ingestion protocols are still needed.

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